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| EXAMINER | |
|---|---|
| CELSA, BENNETT M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1639 | |

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/674,812 | CAPRATHE ET AL. | |
| | Examiner | Art Unit | |
| | Bennett Celsa | 1639 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *20-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 16-19* is/are rejected.

7)☒ Claim(s) *10-15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-35 are currently pending.

Claims 1-19 are under consideration to the extent they read on the elected invention.

Claims 20-35 are withdrawn from consideration as being directed to a nonelected invention.

### *Election/Restriction*

1. Applicant's election with traverse of Group III (claims 1-19, in part) drawn to Formula I compounds, in which Y is an Asp derivative, X is dimethyl cyclohexyl(one) substituted amino sulfoxide (3 structures on pages 94-95) and its use in treating stroke in the correspondence dated 7/9/04 which reads on claims 1-19, is acknowledged.

Applicant argues that public policy (e.g. claim several aspects of their invention together in one application), cost and double patenting considerations merit a withdrawal of the present lack of unity.

This is not persuasive since unity/restriction requirement if proper, does not subvert public policy whether referring to cost or double patenting considerations as argued by applicant.

Applicant further argues that the office action "seems to justify the restriction requirement on the basis of the difficulty of the search" which is improper since the classification system is unreliable and in flux.

This is not persuasive since the restriction was not based solely on search considerations but was based on lack of unity e.g. the lack of a core structure necessary to elicit a common activity (e.g. improper markush). Burdensome search, not solely

relying on classification, was merely ancillary to a finding of a lack of unity in the present case.

Applicant argues that the restriction requirement is improper since the Examiner has failed to demonstrate that the inventions are independent **AND** distinct; and there is no showing of independent inventions.

This is not found persuasive since the present application is a 371 of PCT/US99/09463 and accordingly lack of unity and not restriction applies. In any event it is noted that US restriction practice merely requires a showing of independent **OR** distinct inventions. See MPEP 803.

Applicant argues that formula I represents a "core structure" and then further argues that the Y substituents acids(esters), lactones or CN groups are "not as diverse as the office action has alleged".

This is not found persuasive since a variable (e.g. "Y", R1, R2, R3, R4) can not be considered a core structure since a core structure by its nature is constant (e.g. conserved) not variable. The only constant structure presented by formula I is N-C(=O)(CH)(CH)-C(=O)N which is simply not sufficient core structure to elicit a common utility. There are no examples whatsoever providing evidence that this core structure can function as a substrate (e.g. inhibitor) for IL-1 converting enzyme (ICE). Additionally, applicant is referred to Howard et al. J. Immunology Vol. 147 (9), 2964-9 (11/91) and Mjalli et al. Bioorg. & Med. Chem. Lett. Vol. 5, No. 13 pages 1405-1408 (1995) pages 1405-8 which appear to indicate that more core structure is necessary

e.g. include Asp or a functional equivalent (which would correspond to "Y" variable in present formula I) thereof to bind ICE.

Applicant further argues that when the aspartyl substituent is selected for Y , the X markush substituents only differ by the identity of cyclic structure at the end of the molecule.

In other words applicant is arguing for the rejoinder (in one application) of Groups I-VII. .

This argument was considered and deemed persuasive.

Accordingly, the lack of unity is deemed modified in the following manner:

Group 1, claim(s)1-19(IN PART), drawn to FORMULA I compounds in which Y is an Asp derivative, and 1st method of use in treating stroke.

Group 2, claim(s) 1-5 (IN PART) and 8-19 (IN PART), drawn to FORMULA I compound in which Y is a succinimidyl derivative (second Y structure on page 93) and 1st method of use in treating stroke.

Group 3, claim(s) 1-5 (IN PART) and 8-19 (IN PART), drawn to FORMULA I compound in which Y is a cyano derivative (third Y structure on page 93); and 1st method of use in treating stroke.

Groups 4-6 claim (s) 20-23, drawn to second method of using a compound of one of Groups 1 to 3 above to treat inflammation.

Groups 7-9, claim(s) 24-25, drawn to third method of using a compound of one of Groups 1-3 above to treat septic shock.

Groups 10-12, claim(s) 26-27, drawn to fourth method of using a compound of one of Groups 1-3 above to treat reperfusion injury.

Groups 13-15, claim(s) 28-29, drawn to fifth method of using a compound of one of Groups 1-3 above to treat Alzheimers.

Groups 16-18, claim(s) 30-31, drawn to sixth method of using a compound of one of Groups 1-3 above to treat shigelolosis.

Groups 19-21, claim(s) 32-33, drawn to seventh method of using a compound of one of Groups 1-3 above to treat multiple sclerosis.

Groups 22-24, claim(s) 34-35, drawn to eight method of using a compound of one of Groups 1-3 above to inhibit ICE.

with applicant having elected Group I above.

The requirement, as modified above, is still deemed proper and is therefore made FINAL.

2. Applicant's species election, with traverse, of the compound of Example 31 on page 63 of the specification is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a))

3. Claims 20-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention .

***Allowable Subject Matter***

4. Claims 10-15 are objected to but would be allowable if rewritten or amended to remove nonelected subject matter.

5. The following is an examiner's statement of reasons for allowance: the prior art of record fails to disclose or suggest the specific elected compounds within claims 10-15.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a method of *treating stroke* using a compound of Formula I; the specification does not reasonably provide enablement for *preventing stroke* using the Formula I compounds. The specification does not enable any person skilled in the art to which it pertains; or with which it is most nearly connected, to use the invention as claimed commensurate in scope with these claims.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any experimentation is "undue". These factors include, but are not limited to:

1. The breadth of the claims.

2. The nature of the invention

3. The state of the prior art;

4. The level of one of ordinary skill

5. The level of predictability in the art;

6. The amount of direction provided by the inventor;

7. The presence or absence of working examples;

8. The quantity of experimentation necessary needed to make or use the invention based on the disclosure;

See :*In re Wands* USPQ 2d 1400 (CAFC 1988):

*(1-2) The breadth of the claims and the nature of the invention*:

The claims are directed to a method of treating or preventing stroke comprising the administration to a patient having, having had, or at risk of having a stroke a therapeutically effective amount of a compound of claim 1 or 8

3 and 5) *The state of the prior art and the level of predictability in the art:*

The burden of enabling the prevention of a disease or its symptoms (ie. the need for additional testing) would be greater than that of enabling a treatment due to the need to screen those patients (e.g. mammals i.e. humans) susceptible to such diseases and the difficulty of proof that the administration of the drug composition was the agent that acted to prevent the condition. The specification does not provide guidance as to how one skilled in the art would go about screening those patients susceptible to stroke; nor is guidance provided in the specification as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed composition in preventing stroke.

Additionally, there are no mammalian (e.g. human) genetic markers to enable screening of those mammals genetically predisposed toward a stroke.

(4) *The level of one of ordinary skill in the art:*

The level of skill would be high, most likely at the Ph.D. level.

(6-7) *The amount of direction provided by the inventor and the existence of working examples.*

The specification provides support (e.g. examples) for making formula I compounds (e.g. examples 1-65) along with a generic assertion of the ability of these compounds to act as ICE inhibitors in an *in vitro* "biological" assay. The specification background section further recites the expected ability of ICE inhibitors to treat (NOT PREVENT) diseases associated with interleukin-1 activity which include stroke. There are no specification examples which would be deemed by one of ordinary skill in the art to be correlatable toward PREVENTION of stroke in a mammal (e.g. patient) before onset of the disease.

*(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure:*

*Thus,* the specification discloses only limited examples and in light of the unpredictability and inability of others to effect prevention of stroke, further examples which are reasonably predictive of *in vivo* preventative utility are needed in order to provide the requisite enablement for the presently claimed invention as claimed. Additionally, undue experimentation is necessary to determine screening and testing protocols to demonstrate the efficacy of the presently claimed invention.

***Double Patenting***

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1-9 and 16-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No.6,316,415 (and col. 1 to demonstrate inherent ICE inhibiting capability) in view of WO 98/16502 (3/98).

US Pat. No. 6,316,415 teach ICE (interleukin-1Beta converting enzyme) inhibiting (e.g. see col. 1, especially lines 5-15) compounds of Formula I (e.g. see patent claim 1) of the following general formula:

R1-Asp-CH2-NH-SO2-R2

where R1 is N(R5)(R6)-C(=O)-(A)m- (E.g. see 3rd formula for R1 in patent claim 1);

in which

A is an amino acid selected as alanine, leucine, isoleucine, valine from among 20 amino acids;

m is selected as 1 (from among 0-3)

and R2 is as defined in patent claim 1.

These patented compounds differ from those presently claimed by:

a. Replacing the patent "A" amino acid [e.g. NH-CH (R)-CO where R is hydrogen or lower alkyl] with CH(R)-CH(R)-CO (where R is hydrogen or lower alkyl); and

b. Making pharmaceuticals to treat stroke.

However, the WO 98/16502 reference teaches:

a. the use of ICE inhibiting compounds to treat stroke (e.g. see page 1; claims 1, 23, 30 and 43) and

b. the functional equivalency of substituting an

-amino acid (e.g. "A") at the same position as in the patented compounds [E.g. see claim 43: formula I structure where R1 is -C(=O)-CH(CH3)-NH-C(=O)NH2 on page 164 1st structure]

with CH(R)-CH(R)-CO where R is hydrogen or lower alkyl (see page 164: 5th and 7th structures at @ lines 15-27) at the same position of the patented compound in order to arrive at ICE inhibiting compounds for use as pharmaceuticals for treating stroke.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to modify the patented compounds by replacing the patent "A" amino acid e.g. NH-CH (R)-CO (where R is hydrogen or lower alkyl) with CH(R)-CH(R)-CO (where R is hydrogen or lower alkyl) for use in pharmaceuticals for treating stroke in light of the WO teaching of the functional equivalency of making such a substitution toward obtaining ICE inhibiting compounds for pharmaceutical use in treating stroke with a reasonable expectation of success.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-273-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
August 18, 2004